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EXAMINER	
HIBBERT, CATHERINE S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/535,128	COLLINS ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116,177-182,243-297 and 299-303* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-297, 300 and 302-303* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 177-179,181,182,243,251,252,261,280,289,292,295,299 and 301.

DETAILED ACTION

Claims 1-115, 117-176, 183-242, and 298 are cancelled. Claims 116, 177-182, 243-297, and 299-303 are pending. Claims 177, 178, 179, 181, 182, 243, 251, 252, 261, 280, 289, 292, 295, 299, and 301 are withdrawn. Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-297, 300 and 302-303 are under examination.

Claims 177, 178, 179, 181, 182, 243, 251, 252, 261, 280, 289, 292, 295, 299, and 301 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the species election requirement in the reply filed on 26 February 2009.

Priority

Priority for Claims 300 and 302 is granted only to the US 10/535,128 filing date of 4 April 2006. Support for the taR12 RNA corresponding to SEQ ID NO:55 or the crR12 RNA corresponding to SEQ ID NO: 56 (e.g. instant Claims 300 and 302) in the current claims cannot be found in the PCT/US03/36506, filed 14 November 2003, (hereafter referred to as PCT of 11/14/03) filed 15 November 2002.

Priority for Claims 244-249, 260-264 and 287 and 303 is only granted to the PCT/US03/36506, filed 14 November 2003. Support for any sequences identified by SEQ ID No. (e.g. instant Claims 300 and 302) in the current claims cannot be found in the US Provisional 60/426,891, (hereafter '891 Provisional) filed 15 November 2002. In addition, support for claims 244-249 is not found in the '891 Provisional which only refers to a "100% repression" or a "12X decrease in expression" and a "2-fold increase in GFP expression". In addition, support for the nucleotide sequence lengths of Claims 260-264 and 287 is not found in the '891 Provisional. In

addition, support for the equilibrium association constant of Claim 303 is not found in the '891 Provisional.

Response to Amendment/Argument

Any objections and rejections to cancelled claim 298 are moot.

Any objections and rejections not repeated herein are withdrawn.

The rejection of Claim 116 under 35 U.S.C. 101 is withdrawn based on claim amendments.

Claim Rejections - 35 USC § 112-maintained

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 **stand** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 116, 256, 257, 277, 285 are unclear in what is encompassed by the term "substantially complementary". Although one of ordinary skill in the art would reasonably interpret how the term "substantially complementary" is applied to the comparison of two sequences, such as two stem sequences, in light of the definition provided in the instant specification stating: "Two sequences are considered "substantially complementary" herein if their complementarity is at least 50%" [PgPub I ¶0055], the term "substantially complementary" is unclear in Claims 116, 256, 257, 277 and 285, as written, as applied to embodiments encompassing portions of sequences

which read on single and/or dinucleotide sequences. Therefore, one of ordinary skill in the art would not be able to determine what is encompassed by the term "substantially complementary" with regards to a single base-pair interaction and the metes and bounds of Applicants invention can not be determined.

Applicants' response filed in Remarks of 5/14/2010 have been fully considered. Applicants' response is to traverse by argument and amendment. Applicant argues that claim 116 has added the phrase "at least 6 nucleotides in length" and claims 256, 257, 254, and 284 have added the phrase "at least 4 nucleotides in length" to clarify the claims and that claims 277 and 285 have been amended to remove the phrase "substantially complementary".

Applicants' response has been fully considered but is not persuasive because, for example, the base claim 116 now recites the phrase "and wherein a portion of at least 6 nucleotides in length of the first or second stem-forming portion of the second nucleic acid molecule is complementary or substantially complementary to a portion of at least 6 nucleotides in length of the first nucleic acid molecule". Therefore, the claims are still indefinite because the amendment did not address the term "a portion" and a portion of at least 6 nucleotides or a portion of at least 4 nucleotides still reads on a single nucleotide.

Written Description-maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-297, 300 and 302-303 **stand** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection of cancelled Claim 298 is moot.

Claims are drawn to a gene expression system comprising a genus of a first nucleic acid molecules and a genus of second nucleic acid molecules that are claimed by function and without sufficient structural limitations correlated to the required function.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include:

(1) Actual reduction to practice,

(2) Disclosure of drawings or structural chemical formulas,

(3) Sufficient relevant identifying characteristics such as:

i. Complete structure,
ii. Partial structure,
iii. Physical and/or chemical properties,
iv. **Functional characteristics when coupled with a *known* or *disclosed* structure**, ***and correlation between function and structure***,

(4) Method of making the claimed invention,

(5) Level of skill and knowledge in the art, and

(6) Predictability in the art.

Disclosure of any combination of such identifying characteristics *that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.*" MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not a sufficient characteristic for written description purposes, **even when accompanied by a method of obtaining the claimed sequence**." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant case, the claims are drawn to a system comprising a first and second nucleic acid (RNA) molecule or, regarding Claim 180, to a kit comprising at least an oligonucleotide comprising a crRNA sequence or a taRNA sequence. Regarding the first nucleic

acid molecule, claims are drawn to wherein the molecule comprises a cis-repressive sequence element and wherein the molecule forms ***part*** of a stem-loop structure that represses translation of the ORF. Regarding the second nucleic acid molecule, claims are drawn to wherein the molecule comprises a stem-loop structure and wherein a portion of at least 6 nucleotides in length of the first or second stem-forming portion of the second nucleic acid is complementary or substantially complementary to a portion of at least 6 nucleotides in length of the first nucleic acid molecule and interacts with the first nucleic acid molecule to disrupt the stem-loop structure in which the cis-repressive sequence element participates and thereby derepress translation of the ORF and interacts with the first nucleic acid molecule to derepress translation of the ORF. Therefore, the instant claims require a correlation between the functional requirement of "forming a stem-loop structure" and "acting to repress translation" (i.e. the crR molecules) or to "derepress translation" (i.e. the taR molecules) and the structural requirement of a nucleic acid sequence.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims are broad and generic, with respect to all possible compounds encompassed by the claims. Even the dependent Claim 300 which specifies the SEQ ID NO's 55 and 56 are not remedial because the possible structural variations are limitless to any nucleic acid molecules comprising the designated stem-loop structures. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. In addition, the specification only uses computer programs such

as mFOLD to predict the secondary structures that could possibly form for any given nucleic acid sequence but the actual secondary structure and nucleic acid interactions under various in vitro or in vivo conditions is unpredictable without experimentation such as secondary structure studies and compensatory mutation analysis to verify stem-loop structures predicted by computer programs. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of the taR 12 and crR 12 nucleic acid molecules corresponding to SEQ ID NO's 55 and 56, respectively, and to the nucleic acid molecules identified in the examples by SEQ ID NO, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

Arguments and Response to Arguments

Applicants response (see Remarks filed 5/14/2010) has been fully considered.

Applicants' response is to traverse. Applicants argue that "the subject application provides ample guidance regarding correlations between the function and structure of the claimed systems, such that one of ordinary skill in the art would recognize that the Applicant was in possession of systems encompassed by the claims". Applicants state:

> The subject application teaches nucleic acid based systems that enable post-translational regulation of gene expression. At the RNA level these systems involve pairs of cognate RNA molecules: a cis-repressive RNA molecule (crRNA) and a trans-activating RNA molecule (taRNA). The first of these nucleic acid molecules represses translation of an open reading frame (ORF) while the second interacts with the first nucleic acid molecule in a way that derepresses and thereby activates translation of the ORF. For purposes of illustration, the following paragraphs explain how the structure of an exemplary prokaryotic system from the specification correlates with these repression / activation functions. As will become apparent from this illustration, because these functions result from structural considerations that are driven by well understood and predictable rules (e.g., Watson-Crick pairing), a person of ordinary skill in the art would immediately recognize that these structure / function correlations are generalizable to other systems. This is particularly so when one also considers the extensive guidance that Applicant provides in the specification regarding the design of crRNA structures (see paragraphs

> [0068]-[0099] and [015 7]-[0179] of the published application), the design of cognate taRNA structures (see paragraphs [0100]-[0115] and [0180]-[0187]), and methods for selecting cognate pairs using simple in vitro assays (see paragraphs [0123]-[0128] and [0188]- [0201]).

Applicants specifically points to amended claim 116 and to two diagrams (Remarks, pages 19 and 22) to show a "structure, function and structure / function correlation of the first and second nucleic acid molecules in turn. Applicants argue regarding the first diagram shown on page 19 of Remarks:

> As shown above for an exemplary first nucleic acid molecule, a cis-repressive sequence is strategically introduced upstream of an open reading frame (ORF) of a target gene (e.g., GFP, shown above) or including part of the ORF. The cis-repressive sequence is designed to permit the formation of a stem-loop structure that represses translation of the ORF. As shown above for an exemplary prokaryotic system, the cis-repressive sequence may hybridize through complementary base pairing with the Ribosome Binding Site (RBS) to form the stem while a short intervening sequence forms the loop. In the above example, the stem loop structure that is formed by the cis-repressive sequence sequesters the RBS, thereby preventing ribosome docking and translation initiation. In general however, and as described in the specification, the cis- repressive sequence may be complementary or substantially complementary to any portion of the sequence between the 3' end of the cis-repressive sequence and the 5' end of the ORF (see paragraph [0081]). The stem loop structure may even include a portion of the 5' region of the ORF (see paragraph [0079]). When there is no RBS (e.g., in a eukaryotic system), the cis-repressive sequence may be designed to form a stem-loop structure within the 5' UTR, between the IRES (Internal Ribosome Entry Site) and the 5' end of the ORF and/or encompassing all or part of a Kozak consensus sequence (see paragraph [0079]). In each case, the same correlation links the structure (i.e., sequence) and function (i.e., repressing translation of the ORF) of the first nucleic acid molecule, namely: hybridization of the cis-repressive sequence leads to the formation of a double-stranded stem-loop (hairpin) structure that prevents the ribosome from gaining access to the appropriate location on the mRNA from which to initiate translation from the downstream start codon (see paragraph [0075]).

Applicant continues:

> In general, the sequence (i.e., structure) of putative cis-repressive sequences can be computationally predicted and assembled in solution by generating an initial set of sequences that render the desired stem-loop structure upon folding by Watson-Crick pairing (e.g., with the RBS). In general, optimal cis-repressive sequences will produce a partially unstable stem-loop structure that can be disrupted by a cognate trans-activating

> sequence (the second nucleic acid molecule which is discussed below). The relative stability of different stem-loop structures can be predicted from AG values that can be readily calculated using a variety of computer programs known in the art (see paragraph [0085] and [0108], e.g., the inventors used the Mfold TM program but other programs such as RNAfold TM could also be used). The specification describes how appropriate AG values can be predictably obtained in order to achieve desired levels of hybridization stringency, e.g., by introducing dispersed mismatches and/or inner loops into the sequence (see, for example, paragraphs [0084] and [0105]). It is also worth noting that the settings of computer programs such as Mfold can be adjusted to predict structures and ΔG values under different experimental conditions (e.g., temperature, pH, ionic strength, etc.). Filters can also be applied to exclude putative cis-repressive sequences that would produce more than one predicted secondary structure (see paragraph [0174]). As a result, cis-repressive sequences can be designed that produce predictable structures under the desired experimental conditions.

Thus, Applicants submit:

> From the foregoing it should be readily apparent that the subject application describes a clear correlation between the claimed stem-loop structure of the first nucleic acid molecule and its function of repressing translation of the ORF. Under the Guidelines, this description of a structure function correlation is sufficient to satisfy the written description requirement.

In addition, Applicants argue regarding the second diagram, shown on page 22 of Remarks:

> We now turn our attention to the second (cognate) nucleic acid molecule and explain how its structural features correlate with the claimed derepression (activation) function.
>
> As shown above at the RNA level, the second nucleic acid molecule is a small, non-coding trans-activator (taRNA) that targets the first cis-repressive nucleic acid molecule with high specificity. As described in the specification and as shown above, Watson-Crick base pairing interactions between the first and second nucleic acid molecules permit conformational changes so that a duplex structure forms between the two molecules. In the example above, the duplex structure "disrupts the stem-loop in which the cis-repressive sequence participated, thereby making the region upstream of the ORF accessible to the ribosome. [T]he ribosome can now gain entry to the RBS and translation can proceed" (see paragraph [0104]). In general however, and as described in the specification, the trans-activator sequence may be complementary or substantially complementary to any portion of the first nucleic acid molecule that will result in disruption of the stem-loop structure involving the cis-repressive sequence element (including the stem or loop portions of the cis-repressive sequence, see, for example paragraphs [0101]-[0102]). In each case, the same correlation links the structure (i.e., sequence) and function (i.e., derepressing translation of the ORF) of the second nucleic acid molecule, namely: hybridization of a portion of the second nucleic acid molecule to

a portion of the first nucleic acid molecule leads to the formation of a duplex structure that disrupts the stem-loop structure in which the cis-repressive sequence element participated and thereby makes the region upstream of the ORF accessible to the ribosome (see, for example, paragraph [0104]).

As claimed and described above, the second nucleic acid molecule includes a stem-loop structure. This stem-loop structure is included in order to sequester a portion of the second nucleic acid molecule that is complementary or substantially complementary to the first nucleic acid molecule (e.g., a portion of an RBS-like sequence in the illustration above). As discussed in the specification, this reduces the likelihood that free second nucleic acid molecules will bind ribosomes (see paragraph [0174]). As outlined above for the cis-repressive sequence, in general, the structure (i.e., sequence) of the second nucleic acid molecule can be computationally predicted and assembled in solution by generating an initial set of sequences that produce the desired stem-loop structure upon folding by Watson-Crick pairing. As described above for cis- repressive sequences, computer programs (e.g., Mfold TM, RNAfold TM, etc.) can be utilized to predict the secondary structure of the nucleic acid sequences. Generally, optimal sequences are selected from the initial set with the sequence of a cognate cis-repressive sequence in mind. Additionally, the stability of the secondary structure of any given second nucleic acid molecule can be determined (e.g., by AG value calculations under the desired conditions) and compared with the stability of the duplex formed between the first and second nucleic acid molecules.

Secondary nucleic acid molecules that are more stable when duplexed with the first nucleic acid molecule are suitable for use in a claimed system. As described above, in order to achieve an appropriate AG value for desired levels of hybridization stringency, dispersed mismatches and/or inner loops may be introduced into the sequence of the second nucleic acid molecule (see, for example, paragraphs [0084] and [0105]).

From the foregoing it should be readily apparent that the subject application describes a clear correlation between the structural features of the second nucleic acid molecule along with the associated structural changes that result from its hybridization to the first nucleic acid molecule and its function of derepressing translation of the ORF. Under the Guidelines, this description of a structure function correlation is sufficient to satisfy the written description requirement.

Applicants conclude:

Under the Guidelines, the written description requirement is met for the system of claim 116 and its dependent claims if the subject application discloses a correlation between the function of repressing or de-repressing translation and the claimed structures of the first and second nucleic acid molecules, respectively.

As set forth in the specification and outlined above, the subject application discloses and

claims the structural features that are responsible for the claimed functions. Thus the first nucleic acid molecule includes a cis-repressive sequence element that forms part of a stem-loop structure that prevents the ribosome from gaining access to the appropriate location on the mRNA from which to initiate translation from the downstream start codon (e.g., the RBS in our illustration). A portion of the second nucleic acid molecule is complementary or substantially complementary to a portion of the first nucleic acid molecule and interacts with the first nucleic acid molecule to disrupt the stem-loop structure in which the cis-repressive sequence element participated and thereby derepress translation of the ORF.

Crucially, the correlations between the structural features and claimed functions of both nucleic acid molecules are governed by the fundamental rules of Watson-Crick base pairing that are well understood in the art. In fact, they are so well understood that the structures and stabilities of the first and second nucleic acid molecules can be *computationally predicted* using tools that are available in the art. These same tools can also be used to predict whether the cognate pairs will favor the type of duplex formation that will lead to depression of ORF translation.

In addition to providing generally applicable teachings based on well understood correlations between structure and function, the subject application also described how these teachings were actually used by the inventors to generate and test several cognate pairs of nucleic acid molecules, e.g., crR12 and taR12, crR10 and taR10, among others (see Examples 1- 5).

The Examiner states that "the specification only uses computer programs such as Mfold to predict the secondary structures that could possibly form for any given nucleic acid sequence but the actual secondary structure and nucleic acid interactions under various in vitro or in vivo conditions is unpredictable without experimentation such as secondary structure studies and compensatory mutation analysis to verify stem-loop structures predicted by computer programs" (see page 12 of the Office Action). As a result, the Examiner seems to take the position that Applicant was only in possession of the specific cognate pairs that were reduced to practice.

Applicant respectfully submits that in the context of the claimed systems and in view of the disclosed correlations, the Examiner's emphasis on highly stringent systems and disclosure of specific sequences is inappropriate. The fact that all computationally predicted systems might not work in vitro or in vivo without further experimentation does not mean that Applicant was only in possession of systems that were actually reduced to practice. Applying such a high standard would raise the standard for satisfying the written description requirement to reduction to practice which is clearly not the law (e.g., see the Guidelines which explicitly state that the written description requirement can be satisfied by sufficient disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure). Besides, the skilled person would appreciate that in addition to the computational tools described above, interactions

> between cognate pairs of nucleic acid molecules could also be routinely evaluated by methods that were well known in the art and described in the subject application (see, for example, paragraphs [0123]-[0128]). Now that Applicant has described the structural features that are required to produce cognate pairs, the skilled person would immediately recognize that Applicant could have generated additional cognate pairs through routine experimentation, i.e., that Applicant was "in possession" of the claimed invention. The fact that Applicant did not laboriously generate hundreds of additional cognate pairs using these methods would not, in the eyes of the skilled person, suggest that Applicant was any less "in possession" of the claimed invention. Applicant also wishes to point out that, one skilled in the art would recognize that the subject application provides guidance for designing and using cognate pairs that can be tailored to different situations and the needs of the practitioner. For example, as described in the specification, not all cognate pairs that are encompassed by the present disclosure need to be capable of stringent repression. In fact, in certain situations the teachings may be used to create cognate pairs that allow for less stringent repression (e.g., designing a "knock-down" rather than a "knock-out" system as discussed in paragraph [0077]).

Applicants' response has been fully considered but not found persuasive.

Applicants' argument provides for explanations of how applicants' invention would function and demonstrates that the intended use of applicants' invention, as a means for controlling gene expression and specifically for regulating translation of an open reading frame (ORF), requires a correlation of the structure of the claimed nucleic acid molecule cognate pairs to the intended function. However, this argument does not show what required structure would be needed to achieve the required functional claim limitations. Applicant's argument "that in the context of the claimed systems and in view of the disclosed correlations, the Examiner's emphasis on highly stringent systems and disclosure of specific sequences is inappropriate" is not convincing because in order to claim a broad genus of structures having a required functional limitation, one of ordinary skill in the art would need to be able to envision the next species in the genus for the applicant to show possession of the claimed genus of structures. In addition, Applicants' argument that the "fact that all computationally predicted systems might not work in vitro or in vivo without further experimentation does not mean that Applicant was only in

possession of systems that were actually reduced to practice. Applying such a high standard would raise the standard for satisfying the written description requirement to reduction to practice which is clearly not the law" is also not convincing because the MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include:

(1) Actual reduction to practice,

(2) Disclosure of drawings or structural chemical formulas,

(3) Sufficient relevant identifying characteristics such as:

i. Complete structure,
ii. Partial structure,
iii. Physical and/or chemical properties,
iv. **Functional characteristics when coupled with a *known* or *disclosed* structure, *and correlation between function and structure*,**

(4) Method of making the claimed invention,

(5) Level of skill and knowledge in the art, and

(6) Predictability in the art.

Disclosure of any combination of such identifying characteristics *that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient*." MPEP § 2163. Applicant has stated that the claimed structures would need to be determined by computational analysis and trial and error experimentation. Therefore, since it has been clearly established that applicants' claimed nucleic acid structures require precise functional limitations, it is clear that to show possession of the genus of claimed structures applicant must couple the functional characteristic with *a known or disclosed structure* and then make a correlation between function and structure.

Claim Rejections - 35 USC § 102-maintained

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 116, 244-246, 250, 253-260, 262-279, 281-282 286-288, 290-291, 293-294, 297, and 303 **stand** rejected under 35 U.S.C. 102(b) as being anticipated by Argaman and Altuvia in "*fhlA* Repression by OxyS RNA: Kissing Complex Formation at Two Sites Results in a Stable Antisense-Target RNA Complex" (J. Mol. Biol. 2000:Vol. 300, pages 1101-1112). The rejection of cancelled Claim 298 is moot.

Regarding Claims 116, 250, 253, and 256, Argaman et al teach a system for control of gene expression comprising:

(i) a first RNA molecule comprising a cis-repressive RNA sequence element, at least a portion of which is complementary or substantially complementary to a ribosome binding site (RBS), and which is located upstream of and including part of an open reading frame (ORF), wherein the first RNA molecule forms a stem-loop structure that represses translation of the ORF; and (ii) a second RNA molecule, called OxyS RNA, comprising first and second stem-forming portions and a non-stem-forming portion, wherein the non-stem-forming portion connects the 3' end of the first stem-forming portion and the 5' end of the second stem-forming portion to form a loop, and wherein a portion of the second RNA molecule is complementary or substantially complementary to a portion of the first RNA molecule and interacts with the first RNA molecule to derepress translation of the ORF (e.g. see especially Table 1, page 1105). Table 1 (page 1105) shows measuring the level of translation by the B-Galactosidase activity assay using a system comprising a first RNA molecule (the fhlA32-lacZ fusion RNA) and a second RNA molecule (the OxyS RNA). Argaman et al show that without adding OxyS RNA,

the translation of the *fhlA*32-lacZ fusion is repressed in cis. Argaman et al also describe how the translational repression is similar to how the naturally occurring stem-loop hairpin RNA structure located upstream of and including the ORF of the fhlA mRNA translation is repressed in cis . Upon The effect of the OxyS RNA (second RNA molecule) on activation of translation by relieving the translational repression Regarding Claims 244-245, Argaman et al teach that the first RNA in the form of the native *fhlA* mRNA or in the form of their recombinant fhlA32-lacZ fusion construct, represses translation by at least 90% (page 1105, Table 1). Regarding Claim 275, Argaman et al teach that the first RNA molecule forms a single stable stem (page 1107, Figure 7 and legend). Regarding Claim 276, Argaman et al teach that the first RNA molecule represses translation in the absence of a ligand (page 1107, Figure 7 and legend). Regarding Claim 286, Argaman et al teach that the second RNA molecule comprises a portion comprising the sequence YNAR positioned 5' to the 5' portion of the first stem-forming sequence (page 1107, Figure 7 and legend). Regarding Claims 287-288, Argaman et al teach that the length of the stem of the second RNA molecule is between 6 and 50 nucleotides/12 and 30 nucleotides (page 1107, Figure 7 and legend). Regarding Claims 290/291, Argaman et al teach that the two stem-forming portions of the second RNA molecule exhibit between at least 75 and 95% complementarity (page 1107, Figure 7 and legend). Regarding Claims 293-294, Argaman et al teach that the stem of the second RNA molecule has at least two dispersed areas of non-complementarity (page 1107, Figure 7 and legend). Regarding claim 297, Argaman et al teach that the second RNA molecule comprises a ligand binding domain (page 1107, Figure 7 and legend). Regarding Claim 303, Argaman et al teach that the first RNA molecule and the second

RNA molecule have an equilibrium association constant between 0.8×10^7 and 1.5×10^7 kcal/mol (e.g. page 1106, Table 2).

Regarding Claims 254, 255, 258, 259, Argaman et al teach that the first RNA molecule comprises:

(i) a first stem-forming portion; (ii) a second stem-forming portion comprising an RBS, wherein the two stem-forming portions are complementary or substantially complementary, and (iii) a non-stem-forming portion (comprising YUNR) that forms a loop connecting the 3' end of the first stem-forming portion and the 5' end of the second stem-forming portion, wherein the "engineered" RNA molecule forms a stem-loop structure that represses translation when positioned upstream of an ORF (e.g. page 1107, Figure 7 and legend).

Regarding Claim 260, Argaman et al teach that the loop of the first RNA is 4-12 nt in length (page 1107, Figure 7 and legend). Regarding Claims 262-265, Argaman et al teach that the length of the stem of the stem-loop of the first RNA molecule is approximately 19 nucleotides (page 1107, Figure 7 and legend). Regarding Claims 266-274, Argaman et al teach that the first RNA stem-loop molecule has a stem with at least three dispersed bulges and exhibiting approximately 85% complementarity (page 1107, Figure 7 and legend). Regarding Claim 277, Argaman et al teach that the first stem-forming portion of the first RNA molecule comprises a sequence complementary or substantially complementary to **a** sequence in the 5' portion of an ORF (e.g. page 1107, Figure 7 and legend). Regarding Claims 278-279 and 281-282, Argaman et al teach that the first RNA molecule comprises a spacer comprising one or more nucleotides between the 3' end of the second stem-forming portion and a start codon and has between 5 and 50 nucleotides upstream of the 5' end of the first stem-forming portion and at

least one nucleotide at the 5' end of stem-forming portion that does not participate in the stem-loop structure (page 1107, Figure 7 and legend). Regarding Claims 257, Argaman et al teach wherein at least a portion of the first RNA molecule is complementary or substantially complementary to a Kozak consensus sequence (page 1107, Figure 7 and legend).

Arguments and Response to Arguments

Applicants' response is to traverse. Applicant Remarks filed 5/14/2010 have been fully considered. Applicant argues that "Argaman et al. does not anticipate the claimed invention" and submits:

> Argaman et al. describes a natural system in E. coli for regulation of gene expression where OxyS is a small untranslated RNA that is induced in response to oxidative stress. OxyS acts in trans to inhibit translation of two target genes, rpoS and fhlA. Argaman et al. "focus on the repression by OxyS," finding that "kissing complex formation between OxyS and fhlA at two sites results in a stable antisense-target complex" (see paragraph spanning pages 1101-1102). Table 1 (see page 1105) depicts the repression levels of OxyS on various fusion constructs containing the fhlA gene or mutations thereof. Contrary to the Examiner's statement, Table 1 does not show that, without adding OxyS RNA, the translation of the fhlA fusion is repressed in cis. Rather, Table 1 shows that in the absence of OxyS (column labeled pKK177-3), translation occurs, as measured by [3-galactosidase activity. When OxyS is added (column labeled poxyS), translation is repressed, as measured by a decrease in [3-galactosidase activity. More specifically, Table 1A shows that OxyS represses translation of a both wild-type and mutant fhlA fusions, although at varying levels. Table 1B shows that compensatory mutations in OxyS restore or increase repression of the wild-type and mutant fhlA fusions.

Applicant concludes that:

> Applicant submits that Argaman et al. does not teach a system in which a first RNA molecule acts to repress in cis and a second RNA molecule interacts in trans with the first RNA molecule to de-repress translation of the ORF as claimed.

Applicants' arguments have been fully considered but are not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a system in which a first RNA

molecule acts to repress in cis and a second RNA molecule interacts in trans with the first RNA molecule to de-repress translation of the ORF) are not recited in the rejected claim(s) because the claims are directed to a product composition of a first and second nucleic acid molecule and not to a method. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that a system in which a first RNA molecule acts to repress in cis and a second RNA molecule interacts in trans with the first RNA molecule to de-repress translation of the ORF, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Claims 116, 180, 244-245, 250, and 275 **stand** rejected under 35 U.S.C. 102(b) as being anticipated by Altuvia et al in "The Escherichia coli OxyS regulatory RNA represses fhlA translation by blocking ribosome binding" (EMBO: 1998 Vol. 17, No.20, pages 6069-6075).

Regarding base Claim 116 and dependent Claim 250, Altuvia et al teach that both bacterial and mammalian cells represent naturally occurring systems comprising (i) first stem-loop RNAs comprising cis-repressive sequence elements located upstream and/or including part of an ORF that repress translation of the ORF; and (ii) second stem-loop RNAs that are complementary to a portion of the first stem-loop RNAs that interact with the first stem-loop RNAs to derepress translation of the ORF (e.g. page 6069, ¶ 1-2). Altuvia et al teach the first RNA in the form of the native *fhlA* mRNA or in the form of their recombinant fhlA32-lacZ fusion construct. Regarding base Claim 180, Altuvia et al teach cell systems comprising truncated OxyS RNA transcripts in combination with *fhlA*-lacZ fusion transcripts and the (e.g. page 6069, ¶ 4, lines 9-11) and also comprising the X-Gal inducer (e.g. page 6073, ¶ 6, lines 1-5), which reads on a kit, comprising an oligonucleotide comprising "a crRNA sequence", or "a taRNA sequence" or both, and also comprising an inducer. It is noted that the terms "a taRNA sequence" and "a crRNA sequence" are interpreted to read on any dinucleotide sequence of these sequences. Regarding Claims 244-245, Altuvia et al teach that the first RNA in the form of the native *fhlA* mRNA or in the form of their recombinant fhlA32-lacZ fusion construct, represses translation by at least 80%/90% (e.g. page 6070, Table II). Regarding Claims 247-249, Altuvia et al teach that the second RNA (OxyS RNA) activates translation by 19-fold (e.g. page 6070, Table II). Regarding Claim 275, Altuvia et al teach that the first RNA molecule forms a single stable stem (e.g. page 6069, ¶ 4, lines 9-11).

Arguments and Response to Arguments

Applicants Response in Remarks filed 5/14/2010 have been fully considered.

Applicants Response is to traverse. Applicant argues:

> that Altuvia et al. does not anticipate the claimed invention. Similar to Argaman et al. described above, Altuvia et al. describes a natural system in E. coli that regulates gene expression, involving OxyS, which is a small untranslated RNA that is induced in response to oxidative stress. As described above, OxyS acts in trans to inhibit translation of two target genes, rpoS and fhlA. Specifically, Altuvia et al. teaches that "both fhlA and rpoS are repressed by OxyS expressed constitutively from a multi-copy plasmid or from the chromosome." [Emphasis added] Altuvia et al. further points out that "conversely, the two genes are derepressed in an oxyS deletion strain..." [Emphasis added] (see page 6069, second paragraph of the Introduction).
>
> Applicant submits that Altuvia et al. does not teach a system comprising a first and second nucleic acid molecule, wherein the second nucleic acid molecule interacts in trans with the first nucleic acid to derepress translation of the ORF as claimed. Furthermore, the teachings of Altuvia et al. do not read on a kit comprising a taRNA (trans-activating RNA) as claimed.

Applicants' arguments have been fully considered but are not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., wherein the second nucleic acid molecule interacts in trans with the first nucleic acid to derepress translation of the ORF) are not recited in the rejected claim(s) because the claims are directed to a product composition of a first and second nucleic acid molecule and not to a method. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that a system in which a first RNA molecule acts to repress in cis and a second RNA molecule interacts in trans with the first RNA molecule to de-repress translation of the ORF, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

In addition, regarding Applicants' argument that "the teachings of Altuvia et al. do not read on a kit comprising a taRNA (trans-activating RNA) as claimed", Applicants' arguments are not persuasive because the arguments are not commensurate with the scope of the claims, as written. For example, claim 180 read on one or more oligos comprising a crRNA sequence, or comprising a taRNA sequence, where the kit further comprises one of either an inducer, a host cell and/or a buffer. It is noted that the terms "a taRNA sequence" and "a crRNA sequence" may be interpreted to read on any dinucleotide sequence of these sequences. Altuvia et al teach cell systems comprising truncated OxyS RNA transcripts in combination with *fhlA*-lacZ fusion transcripts and the (e.g. page 6069, ¶ 4, lines 9-11) and also comprising the X-Gal inducer (e.g. page 6073, ¶ 6, lines 1-5), which reads on a kit, comprising an oligonucleotide comprising "a crRNA sequence", or "a taRNA sequence" or both, and also comprising an inducer.

New grounds of rejection necessitated by amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-297, 300 and 302-303 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Currently amended claim 116 recites the limitation "the stem-loop structure in which the cis-repressive sequence element participates" in lines13-14. There is insufficient antecedent basis for this limitation in the claim because the claim does not previously refer to a "stem-loop

structure in which the cis-repressive sequence element participates" and therefore one of ordinary skill in the art would not be able to determine the metes and bounds of applicants' invention. In addition, Claims 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-297, 300 and 302-303 are indefinite insofar as they depend from claim 116.

State of the Art

An oligonucleotide consisting of SEQ ID NO: 55 and an oligonucleotide consisting of SEQ ID NO:56 are free of the prior art.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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